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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,394	03/29/2002	Haifeng Chen	226272007801	5216

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MORRISON & FOERSTER LLP
755 PAGE MILL RD
PALO ALTO, CA 94304-1018

EXAMINER	
MARVICH, MARIA	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 02/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,394	CHEN ET AL.	
	Examiner	Art Unit	
	Maria B Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *19-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8-18 and 24-31* is/are rejected.

7)☒ Claim(s) *6 and 7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/12/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment filed 7/15/04, a supplemental amendment filed 8/12/04 and an amendment filed 12/3/04. In the amendment filed 7/15/04, claims 1-7, 11, 12, 14-16 and 24 have been amended and claims 25-31 have been added. Claims 19-23 are withdrawn from consideration. In the supplemental amendment filed 8/12/04, claims 2, 3, 5, 6 and 24 have been amended.

Claims 1-18 and 24-31 are under examination in this office action.

Response to Amendment

Any rejection of record in the previous action not addressed in this office action is withdrawn. There are new grounds of rejection herein that were not necessitated by applicants' amendment and therefore, this action is not final.

Information Disclosure Statement

An IDS filed 1/12/05 has been identified and the documents considered. The signed and initialed PTO Form 1449 has been mailed with this action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This is a new rejection necessitated by applicants' amendment.**

Claim 5 is vague and indefinite in that the metes and bounds of the term "essentially" are unclear. The term "essentially" is a relative one not defined by the claim, no single set of conditions is recognized by the art as being "essentially" and because the specification does not provide a standard for ascertaining the requisite degree, the metes and bounds of this claim cannot be established.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4 and 25-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Natsoulis (US 5,622,856; see entire document). **This is a new rejection.**

Natsoulis et al teach methods of producing rAAV using a helper construct, pGN1909, comprising rep and cap. The p5 promoter is deleted from the vector and replaced with a FRT sequence (see e.g. fig 2). In the absence of the p5 promoter there is no expression of Rep and Cap.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 8-10, 12, 14-18 and 24-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Salvetti et al (US 6,509,150; see entire document) in view of Mountz and Zhang (US 5,589,377; see entire document). **This is a new rejection.**

Applicants claim an adenovirus vector for the manufacture of rAAV wherein the p5 promoter has been deleted or effectively deleted.

Salvetti et al teach methods for producing and characterizing rAAV using a rep-cap plasmid and an adenovirus helper vector (see e.g. col 7, line 1-13). Nucleotides 190-2278 comprising the rep gene was isolated from wtAAV, accordingly the rep and cap sequences are presumed to be from the same serotype (see e.g. col 7, line 34-35). The p5 promoter was deleted from the rep-cap plasmid or substituted with a heterologous promoter for lower expression of rep (see e.g. col 22, line 7-24 and col 26, line 51-53). In the instance that the p5 promoter is deleted, there is no expression of rep and less than 10% of rep produced in the wild-type cell would be expected.

Salvetti et al do not teach that the rep and cap coding sequences are encoded on an adenovirus vector.

Mountz and Zhang teach methods of producing large-scale rAAV stocks using an Ad vector comprising the rep and cap coding sequences (see e.g. figure 1). Mountz and Zhang teach

that rAAV is currently produced by co-transfecting cells with rAAV and a vector comprising the coding sequences for rep and cap and subsequently infecting with the ad vector. The AdAAV vector was designed to overcome a limitation affecting the production of rAAV, that of finding the optimal ratio of ad vector to AAV rep and cap vector (see e.g. col 1, line 50-67). The resulting AdAAV was used to infect 293 cells to produce rAAV (see e.g. col 14, line 59-67). The rep and cap genes isolated from AAV psub201 and presumed to be from the same serotype were inserted into either the same or different loci of ad such as E1 and E3 (see e.g. col 13, line 20-25 and figure 1A, 8A and 11A). Furthermore, to enhance production of rAAV, expression of rep is attenuated in order to enhance rAAV production (see e.g. col 16, line 52-60). Multiple helper genes are available such as E1A, E1B, E2A and VAI (see e.g. col 7, line 62-67).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the rep and cap plasmid separate from the ad vector taught by Salvetti et al with the AdAAV vector taught by Mountz and Zhang et al because Salvetti et al teach that it is within the ordinary skill of the art to produce rAAV suing a rep cap plasmid and an adenoviral vector and because Mountz and Zhang teach that it is within the ordinary skill of the art to use an AdAAV vector to do so. One would have been motivated to do so in order to receive the expected benefit of overcoming the limitations affecting the production of rAAV with two separate vectors and generating an optimal ratio of ad vector to AAV rep and cap vector (see Mountz and Zhang, col 1, line 50-67). Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Salvetti et al (US 6,509,150; see entire document) in view of Mountz and Zhang (US 5,589,377; see entire document) in view of Rabinowitz et al (US 6,491,907; see entire document). **This is a new rejection.**

Applicants claim a method of producing rAAV in which the rAAV genome is stably integrated into the genome and the cells are infected with a rAd expressing rep and cap. The rep and cap coding sequences can be from different serotypes.

The teachings of Mountz and Zhang and Salvetti et al are described above and are applied as before except:

Neither Mountz and Zhang nor Salvetti et al teach that the rep and cap sequences are from different serotypes.

Rabinowitz et al teach the production of AAV vectors for transduction of heterologous genes into cells. The hybrid parvoviruses comprise cap sequences that are from different serotypes (see e.g. col 11, line 18-40). In this way, the resultant particles have altered antigenic properties, packaging capabilities and tropism (see e.g. col 5, line 40-53).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the rep and cap sequences from the same serotype as taught by Salvetti et al in view of Mountz and Zhang with the rep and cap sequences from different serotypes as taught by Rabinowitz et al because Salvetti et al in view of Mountz and Zhang teach that it is within the ordinary skill of the art to express and produce rAAV in a cell using a vector expressing rep and cap from the same serotype and because Rabinowitz et al teach that it is within the ordinary skill of the art to use rep and cap sequences from different serotypes to

produce AAV vectors. One would have been motivated to do so in order to receive the expected benefit of the resultant particles having altered antigenic properties, packaging capabilities and tropism. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable Salvetti et al (US 6,509,150; see entire document) in view of Mountz and Zhang (US 5,589,377; see entire document) in view of Lebkowski et al (US 5,589,377; see entire document). **This is a new rejection.**

Applicants claim a method of producing rAAV in which the rAAV genome is stably integrated into the genome and the cells are infected with a rAd expressing rep and cap.

The teachings of Mountz and Zhang and Salvetti et al are described above and are applied as before except:

Neither Mountz and Zhang nor Salvetti et al teach that the rAAV genome is integrated into the chromosome.

Lebkowski et al teach methods of producing rAAV for production of large amounts. Lebkowski et al generate permanent cell lines containing a cloned rAAV genome as it can be used continually as a stable, reliable, structurally stable source of rAAV (see e.g. col 5, line 45-61).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to integrate the rAAV genome taught by Salvetti et al in view of Mountz and Zhang as

taught by Lebkowski et al because Salvetti et al in view of Mountz and Zhang teach that it is within the ordinary skill of the art to express and produce rAAV in a cell and because Lebkowski et al teach that it is within the ordinary skill of the art to use an integrated rAAV genome to do so. One would have been motivated to do so in order to receive the expected benefit of generating permanent cell lines containing a cloned rAAV genome as it can be used continually as stable, reliable, structurally stable source of rAAV. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over Salvetti et al (US 6,509,150; see entire document) in view of Mountz and Zhang (US 5,589,377; see entire document) in view of ; see entire document). **This is a new rejection.**

Applicants claim a method of producing rAAV in which the rAAV genome is stably integrated into the genome and the cells are infected with a rAd expressing rep. Rep 78 and 68 are expressed at lower levels than rep 52 and 40.

The teachings of Mountz and Zhang and Salvetti et al are described above and are applied as before except:

Neither Mountz and Zhang nor Salvetti et al teach that rep 78 and 68 are expressed at lower levels than rep 52 and 40.

Snyder teaches methods for increasing rAAV production by engineering low levels of rep78/68 protein expression transcriptionally (see e.g. abstract). Simultaneously, expression of rep52 and 40 is increased (see e.g. col 4, line 6-19). For example expression of rep78/68 can be regulated by tightly controlled expression systems that result in low levels of the proteins (see

e.g. col 8, line 1-3). Under this system increased synthesis of viral capsid proteins and replication of viral DNA results in production of high titre rAAV (see e.g. bridging paragraph col 3-4).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to increase the expression of rep52 and 40 in the vectors taught by Salvetti et al in view of Mountz and Zhang as taught by Snyder because Salvetti et al in view of Mountz and Zhang teach that it is within the ordinary skill of the art to clone and express rep on plasmids and because Snyder teaches that it is within the ordinary skill of the art to clone and express rep78 and 68 separately from rep52 and 40. One would have been motivated to do so in order to receive the expected benefit of increased synthesis of viral capsid proteins and replication of viral DNA results in production of high titre rAAV. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

Claims 1-5, 8-18 and 24-31 are rejected.

Claims 6-7 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1636

February 11, 2005

GERRY LEFFERS
PRIMARY EXAMINER